K001032

JUL 2 4 2000

SUMMARY OF SAFETY AND EFFECTIVNESS INFORMATION

I. Identification of Submitter and Contact, and Date of Preparation

A. Submitter and Owner of the 510(k):

Otsuka Pharmaceutical Co., Ltd.
3-2-27 Ote-dori
Chuo-Ku
Osaka , 540-0021 Japan

B. Official Correspondent:

James W. Harris, Ph.D.
Director of Regulatory Compliance
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C. Date of Preparation:

July 17, 2000

II. Name of the Device

A. Trade/Proprietary Name:
RLP-Cholesterol Immunoseparation Assay (RLP-Cholesterol Assay)

B. Common/Usual Name:
Remnant Lipoprotein Cholesterol (RLP-C) Immunoseparation Reagent Test System

C. Classification Name:
21 C.F.R. 862.1475 Lipoprotein Test System

III. Reason for Submission and Predicate Devices

Otsuka America Pharmaceutical, Inc. (OAPI) is submitting this 510(k) to add a new indication for use to its in vitro diagnostic device known as the RLP-Cholesterol Assay. FDA cleared this device as an aid for the diagnosis of familial type III hyperlipoproteinemia on August 20, 1999 (K991083). OAPI is submitting this 510(k) to add a second indication for use; namely, the RLP-Cholesterol Assay aids in the assessment of CHD risk. For this use, the assay is used in addition with other standard lipoprotein measures. This summary addresses only this second use.

For this second use, the predicate devices are the Direct LDL Cholesterol Immunoseparation Reagent Kit (K943150) and the PBI Plus HDL Precipitation Reagent (K941744).

V. Description of the Device

The RLP-Cholesterol Assay uses two mouse monoclonal antibodies to isolate remnant lipoproteins. The first one (JI-H) is raised against human apo B-100 to remove LDL, Lp(a) and nascent VLDL. The second one (H-12) is raised against human apo A-I to remove HDL. The monoclonal antibodies are conjugated to sepharose-4B beads to separate bound lipoproteins from the remnant lipoproteins that remain in the unbound fraction. Cholesterol in the unbound fraction (RLP-C) is then quantified by an enzymatic assay.

V. Intended Use and Indication

The intended use of the RLP-Cholesterol Assay is to separate and measure lipoproteins in order to characterize the specific type of lipid disorder and to assess coronary heart disease risk. The specific indication [identified as the "intended use" on the device's labeling, as required by 21 C.F.R. § 809.10(a)(2)] is:

> The RLP-Cholesterol Immunoseparation Assay is intended for use in the quantitative determination of cholesterol contained in remnant lipoproteins in human serum or plasma. The test results are used
>
> (1) in conjunction with clinical evaluation, patient risk assessment and other lipoprotein tests as an aid in the assessment of coronary heart disease risk for individuals who have triglyceride concentrations < 800 mg/dL, and
>
> (2) in combination with total serum triglyceride measurements as an aid in the diagnosis of familial type III hyperlipoproteinemia in individuals who have serum total cholesterol concentrations > 200 mg/dL and triglyceride concentrations between 200 and 800 mg/dL.

The predicate devices are the Direct LDL Cholesterol Immunoseparation Reagent Kit (Direct LDL), and the PBI Plus HDL Precipitation Reagent (PBI Plus HDL). The RLP-Cholesterol Assay and the predicate devices do not have identical indication statements, known as "intended use" on the devices' labeling.

The indication statement for the Direct LDL is:

> For use in the direct quantitative determination of low density lipoprotein (LDL) cholesterol in serum or plasma.

The indication statement for the PBI Plus HDL Reagent is:

> For the quantitative determination of high density lipoprotein cholesterol for use in clinical laboratories.

To fully assess the indication of certain *in vitro* devices, however, it is important to look at other parts of the labeling. For example, the device labeling for each predicate device describes its association with the pathogenesis of coronary heart disease (CHD) and coronary artery disease. Specifically, Direct LDL labeling states that increase LDL concentrations are associated with an increased risk of coronary artery disease whereas PBI Plus HDL labeling states that decreased HDL concentrations are associated with an increased risk of CHD.

Although the indication statements in this instance are somewhat different, the intended uses of the devices remain the same; namely, each device is intended to separate and measure a specific lipoprotein to assess the risk for CHD.

VI. Technological Characteristics Compared to the Predicates

The RLP-Cholesterol Assay has different technological characteristics since it measures a different class of lipoproteins compared to the predicate devices. The RLP-Cholesterol Assay and Direct LDL both use immunoseparation principles to separate a fraction of atherogenic lipoproteins. In both devices, the cholesterol content in the isolated fraction is quantified by enzymatic assay. The RLP-Cholesterol Assay uses a different antibody compared to Direct LDL. PBI Plus HDL does not rely upon immunoseparation. Instead, it uses dextran sulfate to precipitate non-HDL lipoproteins. Because of these differences, the performance of the RLP-Cholesterol Assay was evaluated in a series of preclinical and clinical studies.

VII. Performance Tests

OAPI utilized standard laboratory methods to evaluate the technological performance characteristics of the RLP-Cholesterol Assay, and conducted three clinical studies to demonstrate the test's ability to aid in the diagnosis of type III hyperlipoproteinemia. These data were provided in a previous 510(k) submission (K991083).

OAPI conducted four clinical studies to demonstrate that the RLP-Cholesterol Assay is substantially equivalent to the predicate devices in assessing CHD risk.

Study 1 determined the 75th percentile values for fasting and random remnant lipoprotein concentrations (6.6 and 8.8 mg/dL, respectively). These values were used as the cut-off values in the other three studies.

Study 2 was a well-established epidemiological study, which involved 213 subjects with CHD and 2,761 healthy subjects. **Study 3** was a multi-center, case-controlled study involving 150 CHD subjects and 514 controls. **Study 4** was a case-controlled study

specifically designed to study the performance of different lipoprotein tests in assessing CHD risk in African Americans.

These studies showed that RLP-C concentrations were significantly higher, whereas HDL-C concentrations were significantly lower, in CHD subjects. In Caucasians, the mean RLP-C concentrations ranged from 7.2-7.9 mg//dL in control subjects and from 9.4-9.9 mg/dL in subjects with CHD or coronary stenosis. RLP-C concentrations were not elevated in African Americans with significant coronary stenosis compared to controls, neither were HDL-C concentrations.

Studies 2 and 3 demonstrated that the RLP-Cholesterol Assay had similar sensitivity and specificity as the predicate devices in identifying subjects with CHD. These studies also demonstrated that RLP-C and HDL-C were risk factors for CHD independent of age, gender, cigarette smoking, obesity and LDL-C. Elevated RLP-C concentrations were associated with approximately 50% increase in CHD risk ($p < 0.05$), whereas decreased HDL-C concentrations were associated with up to 1-fold increase in CHD risk ($p < 0.01$). LDL-C was not a significant risk factor for CHD in both studies. Study 3 also showed that some subjects with CHD had elevated RLP-C concentrations, but otherwise had normal lipoprotein concentrations. The RLP-Cholesterol Assay identified up to 11% of subjects with CHD who were not recognized by any of the lipid tests recommended by the National Cholesterol Education Program.

IX. Overall Conclusions

The performance data clearly demonstrate that the RLP-Cholesterol Assay is substantially equivalent to the predicate devices. Three clinical studies with different study designs and populations provided consistent results and demonstrated that the RLP-Cholesterol Assay performed as well as the predicate devices in assessing the risk for CHD. These studies also showed that elevated RLP-C levels were an independent risk factor for CHD.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUL 2 4 2000

James Harris, Ph.D.
Director of Regulatory Compliance
Otsuka America Pharmaceutical, Inc.
2440 Research Boulevard
Rockville, Maryland 20850

Re: K001032
Trade Name: RLP-Cholesterol Immunoseparation Assay
Regulatory Class: I reserved
Product Code: CHH
Dated: June 26, 2000
Received: June 29, 2000

Dear Dr. Harris:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K001032

Device Name: RLP-Cholesterol Immunoseparation Assay

Indications for Use:

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(1) in conjunction with clinical evaluation, patient risk assessment and other lipoprotein tests as an aid in the assessment of coronary heart disease risk for individuals who have triglyceride concentrations < 800 mg/dL, and

(2) in combination with total serum triglyceride measurements as an aid in the diagnosis of familial type III hyperlipoproteinemia in individuals who have serum total cholesterol concentrations > 200 mg/dL and triglyceride concentrations between 200 and 800 mg/dL.

Joan Cooper

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K001032

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ OR Over-The-Counter Use ____